REMARKS

Reconsideration of this application is requested. Claims 1-14 and 20-27 are in the case.

I. THE 35 U.S.C. 112, SECOND PARAGRAPH, REJECTION

Claims 1-14 and 20-27 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for the reasons stated on pages 2 and 3 of the Action. Those rejections are respectfully traversed.

In paragraph 1, the Examiner has objected to the term "protected". Without conceding to the merit of this objection, claim 1 has been amended to remove reference to protected derivatives.

In paragraph 2, the Examiner has raised objections with respect to "alkyl". In response, claim 1 has been amended to incorporate the definitions of "alkyl" and "alkylene", as set forth at page 8, line 25 through page 9, line 15.

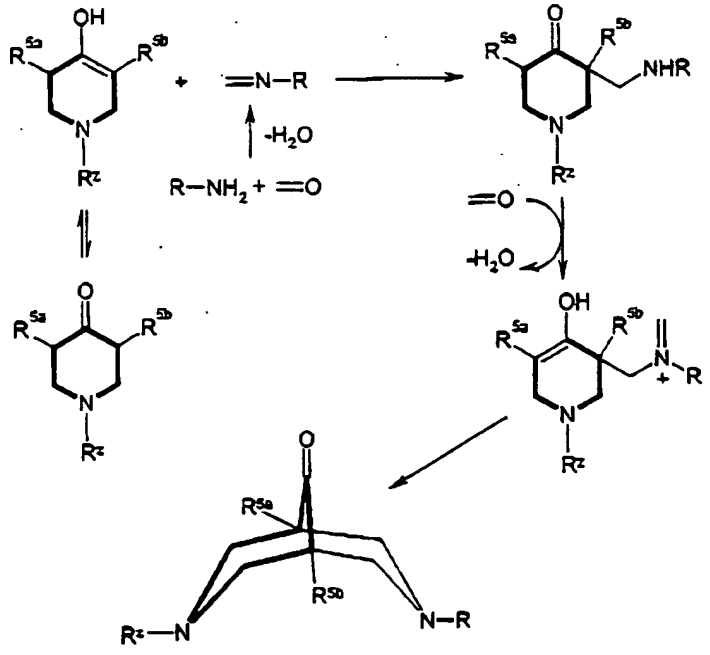
With regard to paragraph 3, claim 20 has been amended to replace "a person suffering from, or susceptible to, such a condition" with "a person in need thereof". Withdrawal of this aspect of the formal rejection is now respectfully requested.

With regard to paragraph 4, it is not understood why the Examiner continues to make this rejection, since claims 22-24 are in a different category to claim 21 (i.e. they are claims to compounds instead of claims to processes), and thus cannot be dependent on claim 21. The dependency is to provide claim definitions without creating a claim dependency in the traditional sense of that term. However, in order to reduce the issues and expedite allowance, claims 22 and 24 have been amended to replace

the references to claim 21 with the definitions provided in that claim. Withdrawal of this aspect of the rejection is now respectfully requested.

With regard to paragraphs 5 and 6, claim 26 has been amended to delete the remaining brackets. In addition, the phrase "in all cases" has been deleted.

With reference to paragraph 7, the Examiner alleges that claim 26 is unclear because it is not possible to use formaldehyde to produce compounds in which R^2 and R^3 represent methyl. It is important to understand the chemistry involved in the processes of claim 26. Thus, first, the substituents R^2 and R^3 are not present in compounds with formulae VIII and XVII, which are bispidone derivatives. Secondly, the formaldehyde is incorporated into the part of the bispidine ring system that is unsubstituted, as set out in the reaction scheme below:



Withdrawal of the rejection set forth in paragraph 7 is now believed to be in order, and is requested.

With reference to paragraph 8, the Examiner alleges that claim 21 is improperly dependent on claim 1, as it is believed that the bispidine *N*-oxide and quaternary ammonium salts are not protected forms of compounds of formula I, as defined in claim 1. In response, claim 21 is not dependent upon claim 1, as it relates to processes and not compounds. This point is discussed earlier in this response. However, in order to further clarify the claims, claim 1 has been amended to include *N*-oxide and quaternary ammonium derivatives of compounds of formula I (see page 8, lines 1-7 of the application as originally filed).

Withdrawal of the outstanding 35 U.S.C. § 112, second paragraph, rejection is now believed to be in order. Such action is respectfully requested.

II. THE 35 U.S.C. § 112, FIRST PARAGRAPH, REJECTIONS

Claim 21 stands rejected under 35 U.S.C. § 112, first paragraph, on alleged lack of enablement grounds with respect to the scope of (r). That rejection is respectfully traversed.

As the term "conversion" can be construed to include multi-step processes, the skilled person would know of methods that could be utilized to convert any given R^6 group to any other given R^6 group. For example, with respect to the conversions mentioned by the Examiner, Applicants point out the following:

(i) The conversion of methyl to ethyl could take place directly by reaction of the methyl compound with a strong base (e.g. an alkyllithium) and a methylating agent (e.g. dimethylsulfate). Deprotonation (and hence methylation) of the compound of

formula I would take place selectively at the methyl substituent on the benzene ring because benzylic protons are more acidic than the protons of normal alkyl or alkylene groups.

The enclosed copy of page 222 from the third edition of "Advanced Organic Chemistry" by Jerry March (published 1985) illustrates the fact that the skilled person would have been well aware of the relative acidity of benzylic protons. With this in mind, it is clear that the skilled person would therefore have arrived at the methylation procedure described above (which utilizes standard reagents and conditions) without any specific guidance from the specification of the present case.

(ii) The conversion of methyl to nitro could take place *via*: (1) oxidation of the methyl group to an aldehyde or an acid; (2) conversion of the aldehyde or acid to a nitrogen-containing derivative; (3) rearrangement of the nitrogen-containing derivative to give an amino group; and (4) oxidation of amino to nitro.

Steps (1) to (4) are all standard and well known to those skilled in the art. Copies of pages 983 to 989 of "Advanced Organic Chemistry" (3rd edition) are attached by way of evidence for the standard nature of the rearrangement of step (3).

As an alternative to steps (3) and (4), the skilled person could instead choose to use the nitrosative decarboxylation procedure described in the enclosed copies of pages 507 and 508 of the 3rd edition of "Advanced Organic Chemistry" (see, in particular, the first full paragraph on page 508), followed by oxidation of the resulting nitroso group (to give a nitro group) under standard conditions.

Withdrawal of the 35 U.S.C. § 112, first paragraph, rejection in regard to the scope of (r) is now believed to be in order. Such action is respectfully requested.

Claims 1-14 and 20-26 stand rejected under 35 U.S.C. § 112, first paragraph, on

alleged lack of enablement grounds with respect to solvates. Without conceding to the merit of this rejection, the claims have been amended to remove reference to "solvates". Withdrawal of this rejection is now respectfully requested.

III. DOUBLE PATENTING

Claims 1-14 and 20-27 stand rejected on alleged obviousness-double patenting grounds over claims 1-26 of copending application Serial No. 09/.623,705. Without conceding to the merit of this rejection a Terminal Disclaimer executed by the undersigned is attached hereto, together with the requisite fee. Withdrawal of this rejection is now respectfully requested.

Allowance of the application is awaited.

Respectfully submitted,

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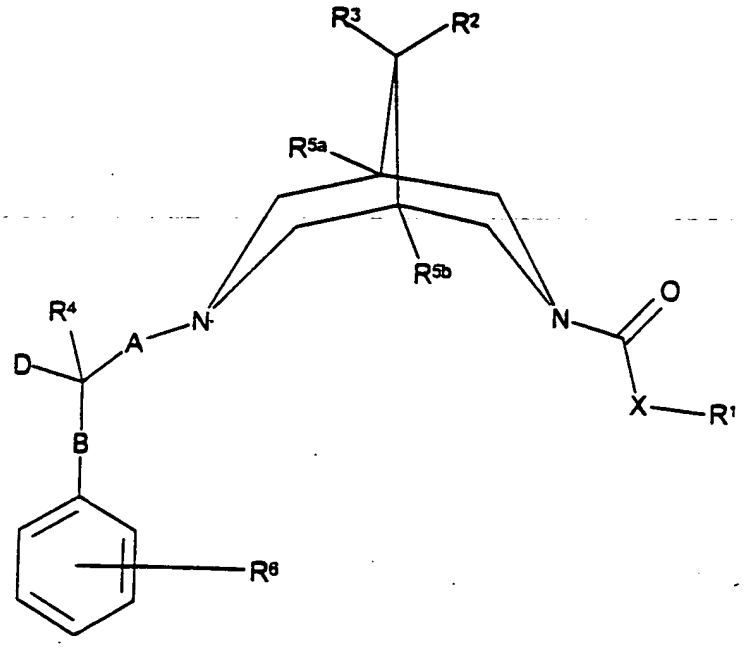
VERSION WITH MARKINGS SHOWING CHANGES MADE

IN THE CLAIMS

1 (Twice amended). A compound of formula I,



I

wherein

R^1 represents C_{1-12} alkyl, $-(CH_2)_a$-aryl, or $(CH_2)_aHet^1$ (all of which are optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy);

a represents 0, 1, 2, 3, or 4;

Het^1 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

X represents O or S;

R^{5a} and R^{5b} independently represent H or C_{1-3} alkyl;

R^2 and R^3 independently represent H, C_{1-4} alkyl (optionally substituted with one or more nitro or cyano groups), OR^7, $N(R^{7a})R^{7b}$, $OC(O)R^8$ or together form $-O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$;

R^7 and R^8 independently represent H, C_{1-6} alkyl or $-(CH_2)_b$-aryl (which latter two groups are optionally substituted by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy);

R^{7a} and R^{7b} independently represent H or C_{1-6} alkyl;

b represents 0, 1, 2, 3 or 4;

R^4 represents H or C_{1-6} alkyl;

D represents H, -OH, or $-(CH_2)_cN(R^{10})(R^{11})$;

c represents 0, 1, 2, 3 or 4;

R^{10} represents H, C_{1-6} alkyl, $-(CH_2)_d$-aryl, $-C(NH)NH_2$, $-S(O)_2R^{13}$, $-[C(O)]_eN(R^{14})(R^{15})$, $-C(O)R^{16}$ or $-C(O)OR^{17}$;

e represents 1 or 2;

R^{11} represents H, C_{1-6} alkyl, $-C(O)R^{18}$ or $-(CH_2)_f$-aryl (which latter group is optionally substituted by one or more substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

R^{14}, R^{15}, R^{16}, R^{17} and R^{18} independently represent H, C_{1-6} alkyl, Het^2 or $-(CH_2)_g$-aryl (which latter three groups are optionally substituted by one or more substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

R^{13} represents C_{1-6} alkyl, aryl or $-(CH_2)_h$-aryl (all of which are all optionally substituted by one or more substituents chosen from halo, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

d, f, g and h independently represent 0, 1, 2, 3 or 4;

Het^2 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R^6 represents one or more optional substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl (optionally terminated by $-N(H)C(O)OR^{18a}$), C_{1-6} alkoxy, $-C(O)N(H)R^{19}$, $-NHC(O)N(H)R^{20}$, $-N(H)S(O)_2R^{21}$ and/or $-OS(O)_2R^{22}$;

R^{19} and R^{20} independently represent H or C_{1-6} alkyl;

R^{18a}, R^{21} and R^{22} independently represent C_{1-6} alkyl;

A represents a single bond, C_{1-6} alkylene, $-N(R^{23})(CH_2)_j-$, $-O(CH_2)_j-$ or $-(CH_2)_JC(H)(OR^{23})(CH_2)_k-$ (in which latter three groups, the $-(CH_2)_j-$ group is attached to the bispidine nitrogen atom, and which latter four groups are all optionally substituted by one or more OH groups);

B represents a single bond, C_{1-4} alkylene, $-(CH_2)_mN(R^{24})-$, $(CH_2)_mS(O)_n-$, $-(CH_2)_mO-$ (in which three latter groups, the $-(CH_2)_m-$ group is attached to the carbon atom bearing D and R^4), $-C(O)N(R^{24})-$ (in which latter group, the -C(O)- group is attached to the carbon atom bearing D and R^4), $N(R^{24})C(O)O(CH_2)_m-$ or $-N(R^{24})(CH_2)_m-$ (in which latter two groups, the $N(R^{24})$ group is attached to the carbon atom bearing D and R^4);

j, k and m independently represent 0, 1, 2, 3 or 4;

n represents 0, 1 or 2;

R^{23} represents H, C_{1-6} alkyl or

R^{24} represents H or C_{1-6} alkyl;

R^{25} represents H, C_{1-6} alkyl, Het^3 or $-(CH_2)_p$-aryl (which latter two groups are optionally substituted by one or more substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

Het^3 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

p represents 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, [solvate or protected], N-oxide or quaternary ammonium derivative thereof;

wherein alkyl groups that R^1, R^2, R^3, R^4, R^{5a}, R^{5b}, R^6, R^7, R^{7a}, R^{7b}, R^8, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{18a}, R^{19}, R^{20}, R^{21}, R^{22}, R^{23}, R^{24}, R^{25} and D may represent, and with which R^1, R^7, R^8, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{25} may be substituted; and alkoxy groups and R^6 may represent, and with which R^1, R^7, R^8, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{25} may be substituted, may be linear or, when there is a sufficient number (i.e. three) of carbon atoms, be branched and/or cyclic, and wherein, when there is a sufficient number (i.e. four) of carbon atoms, such alkyl and alkoxy groups may also be part cyclic/acyclic, and wherein such alkyl and alkoxy groups may also be saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen and/or substituted by one or more fluoro groups; and

wherein alkylene groups that A and B may represent, and $-(CH_2)-$ containing groups that R^1, R^2 and R^3 (together), R^7, R^8, R^{10}, R^{11}, R^{13}, R^{14}, R^{15}, R^{16}, R^{17}, R^{18}, R^{25}, A, B and D may include, may be linear or, when there is a sufficient number (i.e. two) of carbon atoms, be branched, and wherein such alkylene groups and $-(CH_2)-$ containing

chains may also be saturated or, when there is a sufficient number (i.e. two) of carbon atoms, be unsaturated and/or interrupted by oxygen;

provided that:

(a) when D represents either H or -OH, and R^{5a} and R^{5b} both represent H, then at least one of R^2 and R^3 represents OR^7, $OC(O)R^8$ or C_{1-4} alkyl, which alkyl group is substituted with one or more nitro or cyano groups; and

(b) when D represents -OH or $-(CH_2)_cN(R^{10})R^{11}$ in which c represents 0, then:-

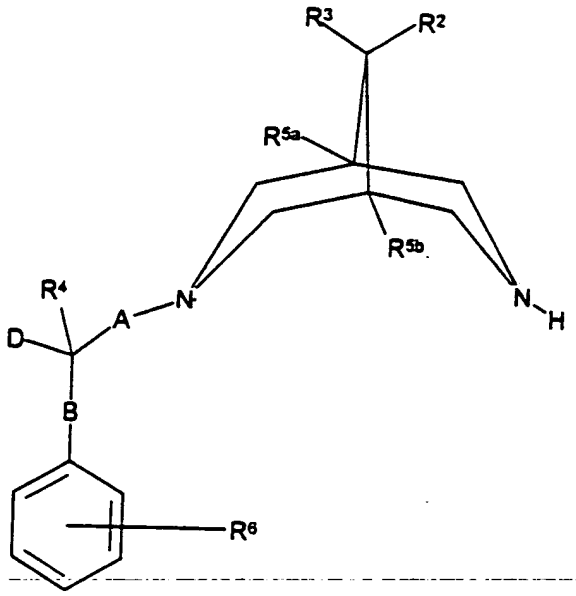
(i) A does not represent $-N(R^{23})(CH_2)_j-$, $-O(CH_2)_j-$ or $-CH_2)_JC(H)(OR^{23})(CH_2)_k-$ (in which k is 0); and/or

(ii) m does not represent 0 when B represents $-(CH_2)_mN(R^{24})-$, $-(CH_2)_mS(O)_n-$ or $-(CH_2)_mO-$.

2 (Amended). A compound as claimed in Claim 1, wherein R^1 represents optionally substituted $-(CH_2)_a$-phenyl, in which a is 0, 1, 2 or 3, or optionally substituted, optionally unsaturated, linear, branched or cyclic, C_{1-18} alkyl (which latter group may also be interrupted by an oxygen atom).

20 (Amended). A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in Claim 1 to a person [suffering from, or susceptible to, such a condition] in need thereof.

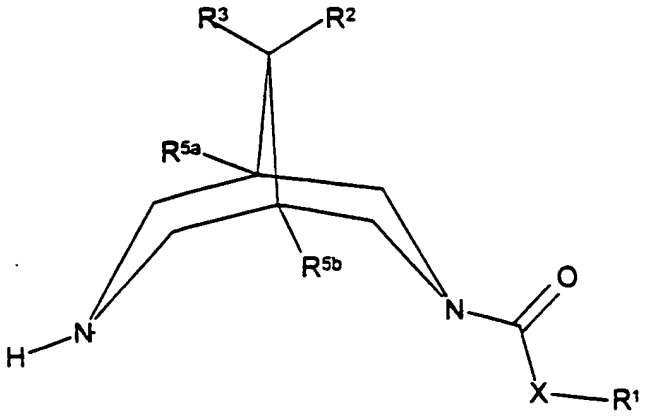
22 (Amended). A compound of formula II [as defined in Claim 21]



II

wherein R^2, R^3, R^4, R^{5a}, R^{5b}, R^6, A, B and D are as defined in Claim 1, or a protected derivative thereof, provided that when R^{5a} and R^{5b} both represent H, then D does not represent H or OH.

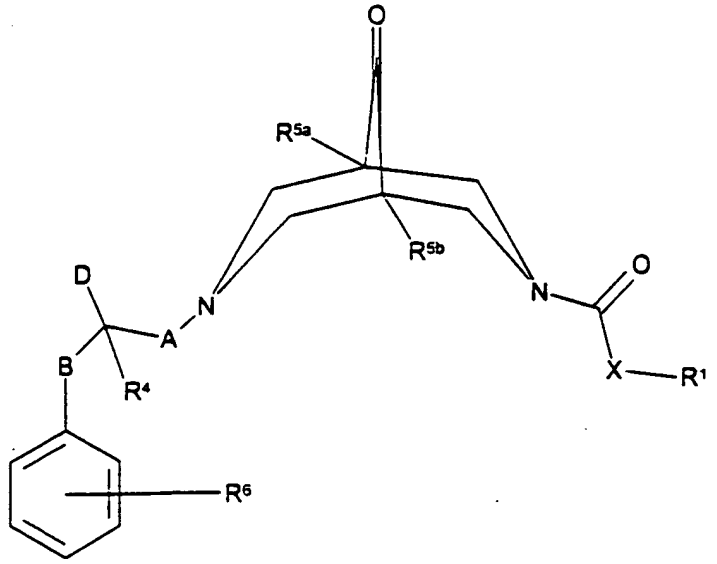
23 (Twice amended). A compound of formula IV [as defined in Claim 21]



IV

wherein R^1, R^2, R^3, R^{5a}, R^{5b} and X are as defined in Claim 1, or a protected derivative thereof, provided that when R^{5a} and R^{5b} both represent H, then at least one of R^2 and R^3 represents OR^7, $OC(O)R^8$ or C_{1-4} alkyl, which alkyl group is substituted with one or more nitro or cyano groups.

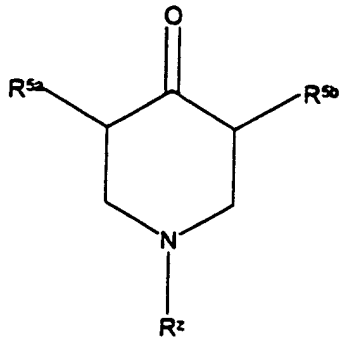
24 (Amended). A compound of formula VIII [as defined in Claim 21]



VIII

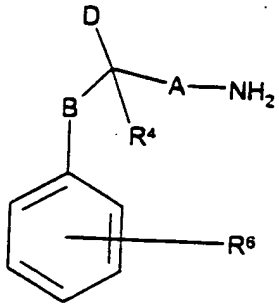
wherein R^1, R^4, R^{5a}, R^{5b}, R^6 A, B, D and X are as defined in Claim 1, or a protected derivative thereof, provided that when R^{5a} and R^{5b} both represent H, then D does not represent H or OH.

26 (Twice amended). A process for the preparation of a compound of formula VIII, as defined in Claim 24, or a compound of formula XVII, as defined in Claim 25, which comprises reaction of a compound of formula XXIX,



XXIX

wherein R^Z represents H or -C(O)XR^1 and R^1, R^{5a}, R^{5b} and X are as defined in Claim 1 with a compound of formula XXX,



XXX

or a protected derivative thereof, wherein R^4, R^6, A, B and D are as defined in Claim 1, [in all cases] in the presence of a formaldehyde.